DETAILED ACTION

Priority

Applicants note that the present application has been accorded the priority of application no. PCT/US98/19437, filed on September 17, 1998, as the earliest priority.

Specification

The disclosure was objected to due to the presence of sequences on pages 2, 14, and 16, without sequence identifiers. In addition, Applicants were requested to correct the address of ATCC.

The foregoing amendments in the specification are believed to overcome these objections.

Claim Rejections - 35 USC § 112

(1) Claims 39-44, 46, 48, and 51-58 were rejected under 35 U.S.C. 112, second paragraph, as "indefinite," in their reference to an extracellular domain lacking its associated signal peptide. Since the claims as currently amended no longer include the language objected to, the present rejection is believed to be moot.

Claim 53 was additionally rejected as "indefinite" in its recitation of thc phrase "stringent conditions." Claim 53 has been canceled, and claim 39 has been amended to recite hybridization under stringent conditions. In addition, claim 39 has been supplemented with actual hybridization and wash conditions. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 39-43 and 52-58 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. The Examiner acknowledged, however, that the specification is enabling "for an isolated polynucleotide having at least 80% nucleotide sequence identity to the polynucleotide encoding SEQ ID NO: 290 or to the nucleic acid encoding the mature form of the polypeptide, which polypeptide induces proliferation of

stimulated lymphocytes in a mixed lymphocyte reaction." Since the claims now recite the indicated biological activity, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(3) Claims 39-43 and 52-58 were rejected for alleged lack of sufficient written description. The Examiner relied on *Vas-Cath* to make it clear that the written description provision of 35 U.S.C. §112 is severable from the enablement provision.

The claims as currently amended recite a high degree of sequence identity with a sequence specifically disclosed in the present application, coupled with a biological property which is sufficiently taught and demonstrated in the present application. In view of this teaching and general knowledge in the art, a person skilled in the art would have reasonably accepted that at the effective filing date of the application Applicants were in the possession of the invention claimed. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections - 35 USC § 102

Claims 52 and 54 have been rejected under 35 U.S.C. 102(e) as "being anticipated" by U.S. Patent 6046030 (We et al., priority date 22 September 1997). The Examiner noted that the rejected claims encompass molecules identified by "hybridization" with no conditions specified. The Examiner added that "[u]nder the appropriate conditions, any DNA will hybridize to any other, and the claims thus are anticipated by any DNA sequence.

Claim 54 has been canceled, and claim 52 has been amended to recite actual stringent hybridization conditions. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection.

Allowable Subject Matter

Claims 45, 47, and 49-51 were objected to as being dependent upon a rejected base claim but were indicated as allowable if rewritten in independent form. Since applicants believe that upon entry of the present amendment all claims will be allowable, the claims objected to have been retained in a dependent form.

Applicants believe that all claims pending in this application are in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Attached to the present Amendment and Response is a marked up copy of the amended claims entitled "**Version with markings to show changes made.**"

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 08-1641 (Docket No.:39780-1618.P2C79). A duplicate copy of this paper is enclosed.

Respectfully submitted,

Date: February 27, 2003

Ginger R. Dreger (Reg. No. 33,055)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

Version with markings to show changes made

In the Specification:

On page 2, the paragraph starting at line 37 was canceled and replaced with the following new paragraph::

--Purification and sequence analysis of the EGF-like domain has revealed the presence of six conserved cysteine residues which cross-bind to create three peptide loops, Savage *et al., J. Biol. Chem.* 248: 7669-7672 (1979). It is now generally known that several other peptides can react with the EGF receptor which share the same generalized motif. Non isolated peptides having this motif include TGF-α, amphiregulin, schwannoma-derived growth factor (SDGF), heparin-binding EGF-like growth factors and certain virally encoded peptides (e.g., Vaccinia virus, Reisner, *Nature* 313: 801-803 (1985), Shope fibroma virus, Chang et al., Mol Cell Biol. 7: 535-540 (1987), Molluscum contagiosum, Porter and Archard, *J. Gen. Virol.* 68: 673-682 (1987), and Myxoma virus, Upton *et al., J. Virol.* 61: 1271-1275 (1987), Prigent and Lemoine, *Prog. Growth Factor Res.* 4: 1-24 (1992).--

On page 14, the paragraph starting at line 25 was canceled and replaced with the following new paragraph:

-- Purification and sequence analysis of the EGF-like domain has revealed the presence of six conserved cysteine residues which cross-bind to create three peptide loops, Savage *CR et al., J. Biol. Chem.* 248: 7669-7672 (1979). It is now generally known that several other peptides can react with the EGF receptor which share the same generalized motif. Non isolated peptides having this motif include TGF-a, amphiregulin, schwannoma-derived growth factor (SDGF), heparin-binding EGF-like growth factors and certain virally encoded peptides (e.g., Vaccinia virus, Reisner AH, *Nature* 313: 801-803 (1985), Shope fibroma virus, Chang W., et al., Mol Cell Biol. 7: 535-540 (1987), Molluscum contagiosum, Porter CD & Archard LC, *J. Gen. Virol.* 68: 673-682 (1987),

and Myxoma virus, Upton C *et al., J. Virol.* 61: 1271-1275 (1987). Prigent SA & Lemoine N.R., *Prog. Growth Factor Res.* 4: 1-24 (1992).--

On page 16, the paragraph starting at line 14 was canceled, and replaced with the following new paragraph:

--The proteins of the TGF-β superfamily are disulfide-linked homo- or heterodimers encoded by larger precursor polypeptide chains containing a hydrophobic signal sequence, a long and relatively poorly conserved N-terminal pro region of several hundred amino acids, a cleavage site (usually polybasic), and a shorter and more highly conserved C-terminal region. This C-terminal region corresponds to the processed mature protein and contains approximately 100 amino acids with a characteristic cysteine motif, *i.e.*, the conservation of seven of the nine cysteine residues of TGF-β among all known family members. Although the position of the cleavage site between the mature and pro regions varies among the family members, the C-terminus of all of the proteins is in the identical position, but differing in every case from the TGF-β consensus C-terminus. Sporn and Roberts, 1990, *supra.* --

On page 252, the first paragraph under the heading of "Deposit of Material" was deleted, and replaced with the following new paragraph:

--The following materials have been deposited with the American Type Culture Collection, Manassas, VA, USA (ATCC):

Material	ATCC Dep. No.	Deposit Date
DNA32292-1131	ATCC 209258	September 16, 1997
DNA33094-1131	ATCC 209256	September 16, 1997
DNA33223-1136	ATCC 209264	September 16, 1997
DNA34435-1140	ATCC 209250	September 16, 1997
DNA27864-1155	ATCC 209375	October 16, 1997
DNA36350-1158	ATCC 209378	October 16, 1997
DNA32290-1164	ATCC 209384	October 16, 1997
DNA35639-1172	ATCC 209396	October 17, 1997

DNA33092-1202	ATCC 209420	October 28, 1997
DNA49435-1219	ATCC 209480	November 21, 1997
DNA35638-1141	ATCC 209265	September 16, 1997
DNA32298-1132	ATCC 209257	September 16, 1997
DNA33089-1132	ATCC 209262	September 16, 1997
DNA33786-1132	ATCC 209253	September 16, 1997
DNA35918-1174	ATCC 209402	October 17, 1997
DNA37150-1178	ATCC 209401	October 17, 1997
DNA38260-1180	ATCC 209397	October 17, 1997
DNA39969-1185	ATCC 209400	October 17, 1997
DNA32286-1191	ATCC 209385	October 16, 1997
DNA33461-1199	ATCC 209367	October 15, 1997
DNA40628-1216	ATCC 209432	November 7, 1997
DNA33221-1133	ATCC 209263	September 16, 1997
DNA33107-1135	ATCC 209251	September 16, 1997
DNA35557-1137	ATCC 209255	September 16, 1997
DNA34434-1139	ATCC 209252	September 16, 1997
DNA33100-1159	ATCC 209373	October 16, 1997
DNA35600-1162	ATCC 209370	October 16, 1997
DNA34436-1238	ATCC 209523	December 10, 1997
DNA33206-1165	ATCC 209372	October 16, 1997
DNA35558-1167	ATCC 209374	October 16, 1997
DNA35599-1168	ATCC 209373	October 16, 1997
DNA36992-1168	ATCC 209382	October 16, 1997
DNA34407-1169	ATCC 209383	October 16, 1997
DNA35841-1173	ATCC 209403	October 17, 1997
DNA33470-1175	ATCC 209398	October 17, 1997
DNA34431-1177	ATCC 209399	October 17, 1997
DNA39510-1181	ATCC 209392	October 17, 1997
DNA39423-1182	ATCC 209387	October 17, 1997
DNA40620-1183	ATCC 209388	October 17, 1997
DNA40604-1187	ATCC 209394	October 17, 1997
DNA38268-1188	ATCC 209421	October 28, 1997
DNA37151-1193	ATCC 209393	October 17, 1997
DNA35673-1201	ATCC 209418	October 28, 1997

DNA40370-1217	ATCC 209485	November 21, 1997
DNA42551-1217	ATCC 209483	November 21, 1997
DNA39520-1217	ATCC 209482	November 21, 1997
DNA41225-1217	ATCC 209491	November 21, 1997
DNA43318-1217	ATCC 209481	November 21, 1997
DNA40587-1231	ATCC 209438	November 7, 1997
DNA41338-1234	ATCC 209927	June 2, 1998
DNA40981-1234	ATCC 209439	November 7, 1997
DNA37140-1234	ATCC 209489	November 21, 1997
DNA40982-1235	ATCC 209433	November 7, 1997
DNA41379-1236	ATCC 209488	November 21, 1997
DNA44167-1243	ATCC 209434	November 7, 1997
DNA39427-1179	ATCC 209395	October 17, 1997
DNA40603-1232	ATCC 209486	November 21, 1997
DNA43466-1225	ATCC 209490	November 21, 1997
DNA43046-1225	ATCC 209484	November 21, 1997
DNA35668-1171	ATCC 209371	October 16, 1997
DNA77624-2515	ATCC 203553	December 22, 1998--

In the Claims:

Claims 48, 53 and 54 have been canceled.

Claims 39-44 and 52 have been amended as follows:

39. (Once amended) An isolated nucleic acid having at least 80% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

40. (Once amended) The isolated nucleic acid of Claim 39 having at least 85% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

41. (Once amended) The isolated nucleic acid of Claim 39 having at least 90% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

42. (Once amended) The isolated nucleic acid of Claim 39 having at least 95% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

43. (Once amended) The isolated nucleic acid of Claim 39 having at least 99% nucleic acid sequence identity to:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

44. (Once amended) An isolated nucleic acid comprising:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290);

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction.

52. (Once amended) An isolated nucleic acid that hybridizes to, under stringent conditions,:

(a) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO: 290):

(b) a nucleic acid sequence encoding the polypeptide shown in Figure 102 (SEQ ID NO 290), lacking its associated signal peptide;

(c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 SEQ ID NO: 290):

[(d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 102 (SEQ ID NO: 290), lacking its associated signal peptide;

(e)] (d) the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289);

[(f)] (e) the full-length coding sequence of the nucleic acid sequence shown in Figure 101 (SEQ ID NO: 289); or

[(g)] (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927;

wherein said polypeptide induces proliferation of stimulated lymphocytes in a mixed lymphocyte reaction, and

wherein said stringent conditions are hybridization in 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.